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DOCUMENT-IDENTIFIER: US 5770429 A

TITLE: Transgenic non-human animals capable of producing heterologous antibodies

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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US-CL-CURRENT: 435/328, 424/184.1 , 435/332 , 435/343.2 , 435/69.1 , 530/387.1 , 530/388.1 , 530/388.15 , 530/388.2 , 536/23.1 , 536/23.53 , 800/6

CLAIMS:

What is claimed is:

1. A monoclonal human immunoglobulin composition free of other human proteins, comprising a human sequence IgG having a binding constant of at least 2.times.10.sup.9 M.sup.-1 for binding to a predetermined human antigen, wherein said immunoglobulin consists of:

a somatically mutated human sequence light chain composed of (1) a light chain variable region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human V.sub.L gene segment and a human J.sub.L segment, and (2) a light chain constant region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human C.sub.L gene segment; and

a somatically mutated human sequence heavy chain composed of a (1) a heavy chain variable region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human V.sub.H gene segment, a D region, and a human J.sub.H segment, and (2) a constant region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human C.sub.H gene segment

wherein the human sequence heavy chain and human sequence light chain are separately encoded by a human heavy chain transgene and a human light chain transgene integrated into a mouse cell genome.

2. The composition of claim 1, wherein the composition comprises a monoclonal antibody of a single idiotype.

3. The composition of claim 1, wherein the predetermined human antigen is a human protein which naturally occurs as a surface or transmembrane protein in at least one cell type of somatic cells of a human.

4. The composition of claim 1, wherein the human sequence light chain has a .kappa. constant region.

5. The composition of claim 1, wherein the human sequence heavy chain has a .gamma. constant region.

6. The composition of claim 1, wherein the immunoglobulin comprises a human sequence light chain having a .kappa. constant region and a human sequence heavy chain having a .gamma. constant region.

7. The composition of claim 3, wherein the predetermined human antigen is a human CD4 protein or antigenic fragment thereof.

8. The composition of claim 6, wherein the predetermined human antigen is a human CD4 protein or antigenic fragment thereof.

9. An immunoglobulin having a binding constant of at least 1.times.10.sup.10 M.sup.-1 for binding to a predetermined human antigen, wherein said inmmunoglobulin is free from other human proteins and is composed of:

a somatically mutated human sequence light chain composed of (1) a light chain variable region having a polypeptide sequene which is substantially identical to a polypeptide sequence encoded by a human V.sub.L gene segment and a human J.sub.L segment, and (2) a light chain constant region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human C.sub.L gene segment; and

a somatically mutated human sequence heavy chain composed of a (1) a heavy chain variable region having a polypeptide sequene which is substantially identical to a polypeptide sequence encoded by a human V.sub.H gene segment, a D region, and a human J.sub.H segment, and (2) a constant region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human gamma isotype C.sub.H gene segment, wherein the immunoglobulin is not from a human B cell.

10. The immunogiobulin of claim 9, wherein the predetermined human antigen is a human protein which naturally occurs as a surface or transmembrane protein in at least one cell type of somatic cells of a human.

11. The immunoglobulin of claim 10, wherein the human protein is human CD4 or an antigenic fragment thereof.

12. The immunoglobulin of claim 9, wherein the human sequence light chain is a .kappa. chain and the human sequence heavy chain is a .gamma. chain.

13. A hybridoma composed of a B cell obtained from a transgenic mouse

having a genome comprising a human heavy chain transgene and a human light chain transgene, said B cell fused to an immortalized cell suitable to generate a hybridoma, wherein said hybridoma produces a detectable amount of the immunoglobulin of claim 10 into culture supernatant.

14. A hybridoma of claim 13, wherein said immunoglobulin consists of a human sequence .kappa. chain and the human sequence .gamma. chain.

15. A hybridoma of claim 13, wherein the immunoglobulin binds to human CD4 with a binding constant of at least 1.1.times.10.sup.10 M.sup.-1.

16. A hybridoma of claim 14, wherein the immunoglobulin binds to human CD4 with a binding constant of at least 1.1.times.10.sup.10 M.sup.-1.

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ABSTRACT:

The invention relates to transgenic non-human animals capable of producing heterologous antibodies and methods for producing human sequence antibodies which bind to human antigens with substantial affinity.

16 Claims, 112 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 93

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US Patent No. - PN (1):
5770429

Detailed Description Text - DETX (219):

Multiple functional YACs having an expanded V segment repertoire may be combined to work with a human Ig transgene (or multiple human Ig transgenes). Although referred to herein as YAC transgenes, such transgenes when integrated into the genome may substantially lack yeast sequences, such as sequences required for **autonomous** replication in yeast; such sequences may optionally be removed by genetic engineering (e.g., restriction digestion and pulsed-field gel electrophoresis or other suitable method) after replication in yeast in no longer necessary (i.e., prior to introduction into a mouse ES cell or mouse prozygote).

Detailed Description Text - DETX (747):

Our results demonstrate that these important cis-acting regulatory elements are either closely linked to individual .gamma. genes, or associated with the 3' heavy chain enhancer included in the HC1 and HC2 transgenes. Because the HC1 and HC2 inserts undergo transgene-**autonomous** class switching--which can serve as a marker for sequences that are likely to have been somatically mutated--we were able to easily find hypermutated transcripts that did not originate from translocations to the endogenous locus. We found somatically mutated .gamma. transcripts in three independent transgenic lines (two HC1 lines and one HC2 line). It is therefore unlikely that sequences flanking the integration sites of the transgene affect this process; instead, the transgene sequences are sufficient to direct somatic mutation.